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Past, present and future of dynamic kidney and liver preservation and resuscitation

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Abbreviations:

CIT	cold ischaemia time
COPE	Consortium for Organ Preservation in Europe
COR	controlled oxygenated rewarming
DCD	donation after circulatory death
DGF	delayed graft function
EAD	early allograft dysfunction
ECD	expanded criteria donor
HMP	hypothermic machine perfusion
HOPE	hypothermic oxygenated perfusion
HRP	hypothermic regional perfusion
MP	machine perfusion
NMP	normothermic machine perfusion
NRP	normothermic regional perfusion
PNF	primary non-function
RCT	randomised controlled trial
RP	regional perfusion
SCS	static cold storage
SMP	subnormothermic machine perfusion

Abstract

The increased demand for organs has led to the increased usage of "higher-risk" kidney and liver grafts. These grafts from donation after circulatory death or expanded criteria donors are more susceptible to preservation injury and have a higher risk of unfavourable outcomes. Dynamic, instead of static preservation could allow for organ optimisation, offering a platform for viability assessment, active organ repair and resuscitation. *Ex situ* machine perfusion and *in situ* regional perfusion in the donor are emerging as potential tools to preserve and resuscitate vulnerable grafts. Preclinical findings have ignited clinical organ preservation research that investigates dynamic preservation, its various modes (continuous, pre-implantation) and temperatures (hypothermic, sub-, or normothermic). This review outlines the current status of dynamic preservation of kidney and liver grafts and describes on-going research and emerging clinical trials.

Introduction

The shortage of suitable organs for transplantation has resulted in the increased use of "higher-risk" grafts. Kidneys and livers from donation after circulatory death (DCD) donors or recovered from brain dead expanded criteria donors (ECD) are particularly susceptible to the harmful effects of warm and cold ischaemia and reperfusion injury. Consequently, these organs have an increased probability to develop initial graft dysfunction (delayed graft function (DGF) in kidney, early allograft dysfunction (EAD) in liver), primary non-function (PNF), biliary complications, and decreased long-term graft survival (1-5). Optimised organ preservation strategies protecting these vulnerable grafts should allow organ viability assessment and resuscitation, thus reducing the unnecessary discard of organs. For this purpose, novel dynamic preservation strategies are being developed.

This overview outlines the current status of dynamic preservation of kidney and liver grafts and describes on-going research and emerging clinical trials. These trials were identified by a thorough search of available online registry databases.

Table S1: Non-exhaustive list of planned or on-going clinical trials investigating dynamic preservation of kidney or liver that were not registered in an online clinical trial registry at the time of writing this manuscript.

Supplementary Appendix *1* outlines the search strategy. Suppl. Table 1 shows a non-exhaustive list of currently non-registered trials identified through our network.

From dynamic to static storage and back

The concept of dynamic organ preservation was developed by Carrel and Lindbergh in the 1930s (6, 7). Some thirty years later, after extensive work by pioneering groups led by Belzer (8-10) and Starzl (11-13), hypothermic dynamic preservation using plasma or blood-based solutions became a clinical reality. Dynamic preservation was the only way to preserve deceased organs until static cold storage (SCS) solutions became available (14-16). SCS offered a simple and effective way to preserve and transport organs, and soon became the most commonly used storage method. Recently, with increasing use of “higher-risk” grafts, there has been a resurgence of interest in dynamic preservation strategies. These could offer optimised organ preservation and real-time graft viability assessment whilst offering a platform for delivery of conditioning agents to repair damaged organs resulting in improved organ quality and utilisation.

Features and modalities of dynamic preservation

During dynamic preservation, recirculating perfusate (either acellular or blood-based) is continuously pumped through the organ vasculature. The perfusate can be non-oxygenated or oxygenated. A heat exchanger regulates temperature from hypothermia via subnormothermia to normothermia. Machine perfusion (MP) perfuses the organ *ex situ*, after it has been procured,

cannulated and connected to a pump (Fig. 1A). Continuous MP (from procurement to implantation) or pre-implantation MP (after a period of SCS and just before transplantation) are most commonly used (Fig. 2). Dynamic preservation can also begin before organ procurement by recirculating donor blood or a preservation solution *in situ,* after cannulation of the aorta/iliac arteries and vena cava/iliac veins (Fig. 1B). The abdominal compartment is isolated from the thorax by a balloon in, or a clamp on, the descending thoracic aorta, preventing cardiac and cerebral perfusion. This technique is also called abdominal regional perfusion (RP).

Key elements determining dynamic preservation modalities are temperature (Fig. 2) and perfusion settings. Hypothermic dynamic preservation aims to slow down cellular metabolism and counteract undesirable and detrimental effects of ischaemia. It combines low temperature (4-10°C) with an acellular colloid-containing preservation solution, in the majority of cases using the Na-gluconate/hydroxyethyl starch machine perfusion solution developed by Belzer et al. (17). There is some evidence that hypothermic dynamic preservation should be pressure- and not flow-controlled, using low pressures to avoid pressure-related injury (18-20). Pulsatile renal artery perfusion (25-30 mmHg) is best for the kidney (20-26). The liver is perfused through the portal vein with a continuous flow, which in most circuits is pressure-controlled (3-5 mmHg, sometimes achieved by gravity) and occasionally flow-controlled (19, 27-33). It is not entirely clear whether portal perfusion alone is sufficient. Maintaining the peri-biliary vascular plexus seems of vital importance in the prevention of ischaemic-type biliary strictures (34). As mainly the hepatic artery supplies this plexus, some authors have advocated dual perfusion (portal vein and hepatic artery) (34). On the other hand, it seems that cold portal vein perfusion allows perfusion of the intra- and extra biliary vascular supply (35). To date, clinical trials have either used single pressure-controlled portal vein perfusion (30, 32), or non-pulsatile flow-controlled dual perfusion (27, 31).

Normothermic dynamic preservation (35-37°C) aims to restore normal cellular processes whilst facilitating viability assessment (36, 37). Normothermic preservation mandates an oxygenated perfusate with an oxygen carrier (usually red blood cells). Compared to hypothermic conditions,

where in the event of pump failure the graft is essentially cold-stored, an organ in a normothermic system is vulnerable to warm ischaemia should machine failure occur. Higher, near-physiological pressures are used for arterial perfusion of kidney (70-85 mmHg) (38-40) and liver (60-105 mmHg) (41-44). Pressure-controlled pumping of pig kidneys resulted in improved renal perfusion and better preserved structural integrity whereas flow-control caused diffuse and global glomerular destruction (40).

Subnormothermic dynamic preservation (20-25°C) aims to avoid cold-induced injury without increasing metabolism to a level where intense oxygenation requires an oxygen carrier. Both acellular and cellular perfusates have been used (45-49). Pressure settings used for perfusion are set at 40 mmHg for kidney (49), 4-8 mmHg for portal vein, and 25-70 mmHg for hepatic artery (46-48, 50).

Controlled oxygenated rewarming, i.e. slowly rewarming a SCS organ to 20°C, aims to avoid abrupt temperature changes. Indeed, a possibly underestimated side effect of quickly rewarming an organ from hypo- to (sub)normothermic conditions may cause a "heat-shock" leading to mitochondrial dysfunction (51).

Ex situ dynamic preservation

Kidney

Non-oxygenated hypothermic machine perfusion

Non-oxygenated hypothermic MP (HMP) of the kidney, at low perfusion pressures (20-30 mmHg), has been shown to reduce DGF, and may improve graft survival (52). The largest randomised controlled trial (RCT) comparing SCS with continuous HMP of deceased donor kidneys using the LifePort (Organ Recovery Systems, Itasca, IL, USA) showed an overall reduced risk of DGF and a survival benefit, the latter most pronounced in ECD kidneys (21, 24). This portable device uses conventional roller-pump technology to generate a pressure-controlled pulsatile flow. Continuous HMP of DCD III (circulatory arrest after withdrawal of treatment) kidneys also resulted in a

decreased risk of DGF, but no impact on graft survival could be demonstrated (22). A parallel trial, also using the LifePort, did not demonstrate a reduction in DGF for DCD III kidneys (23). The use of both continuous and pre-implantation HMP in the latter may be the reason for the discrepancy between these trials. It has been suggested that relatively short periods of HMP (<4h) following long periods of SCS in DCD kidneys has reduced or no benefit compared to continuous HMP (53). Although Watson and colleagues are comparing continuous and pre-implantation HMP to SCS in two on-going trials (Table 1), there are currently no RCTs comparing continuous with pre-implantation HMP.

Furthermore, it is possible that the length of HMP and its protective effect, may be different for different kidney types. Recent large registry analyses (>90,000 kidneys) have shown that in standard criteria kidneys, HMP reduces the risk of DGF compared to SCS irrespective of very short or very long CIT (54). In the same study, the risk of DGF was reduced for ECD kidneys with CIT>6h only, and in the case of DCD with CIT 6-24h only (54). Possibly an effect of shorter pumping times for ECD and DCD may have been missed due to lower numbers in the analyses, however, if this is not the case, then it suggests that these kidneys need to be pumped for at least 6h to benefit from HMP. Nevertheless, as CIT is a well-established predictor of DGF (3), a balance between minimising CIT and any potential benefits of HMP is required. To date, there is a lack of evidence that HMP allows longer duration of CIT. It seems that just a few hours of HMP, as long as the total CIT is not extended, can have a positive impact on early graft function compared to SCS. Additionally, published studies have reported no robust tools for viability assessment during HMP. Although previous studies have shown that increased vascular resistance and high perfusate injury marker concentrations are risk factors for DGF, they are not accurate enough to predict long-term outcomes or justify kidney discard (55, 56). The development of novel biomarker identification platforms, such as proteomics and metabolomics, may allow better assessment.

Oxygenated hypothermic machine perfusion

Oxygenation during HMP appears to be beneficial, as several preclinical studies have shown that cellular metabolism is slower but not at standstill and respiration continues during HMP resulting in oxidative stress (57, 58). Recent comparative porcine studies have demonstrated that, particularly in DCD, oxygenated continuous HMP improves early kidney graft function (59-61). In DBD settings it seems that a short period of oxygenated pre-implantation HMP could be sufficient to improve creatinine clearance when compared to SCS, possibly as effective as continuous oxygenated HMP (62, 63). The ideal oxygen tension, providing balance between benefit of oxygen and risk of increased production of oxygen free-radical species, remains unknown (60, 64).

The effect of oxygenated HMP is being investigated in two RCTs initiated by the Consortium on Organ Preservation in Europe (COPE) (Table 1) using the Kidney Assist (Organ Assist, Groningen, The Netherlands). The Kidney Assist oxygenates the preservation solution and uses a centrifugal pump to generate a pressure-controlled pulsatile flow. COPE-COMPARE randomises one kidney from DCD III ≥50y donors to oxygenated continuous HMP, the other to non-oxygenated continuous HMP. The trial is powered to demonstrate a difference in glomerular filtration 1y post-transplantation, with DGF and graft survival as secondary endpoints (Suppl. Appendix 2). In COPE-POMP, powered to demonstrate a difference in 1y graft survival, ECD kidneys are randomised upon arrival in the recipient centre to a minimum of 2h pre-implantation oxygenated HMP versus continued SCS (Suppl. Appendix 3).

Normothermic machine perfusion

A short period of normothermic MP (NMP) immediately prior to implantation has been found to improve kidney graft function, replenish ATP and reduce injury in a number of large animal models (36). A pilot clinical study compared 18 ECD kidneys that received 1h of pre-implantation blood-based NMP with 47 matched SCS-controls. Remarkably low DGF rates were seen with pre-implantation NMP (5,6% vs. 36,2%) (38). Currently, there are no registered on-going RCTs comparing

pre-implantation NMP to SCS. In contrast to HMP, kidney function can be evaluated during NMP by assessing macroscopic appearance of blood perfusion, renal blood flow and urine output (65, 66), but proof of concept of transplanting kidneys that were discarded and subsequently resuscitated by pre-implantation NMP has not yet been reported. Developing and validating tools assessing graft quality, predictive of transplant outcome, are needed to aid decision-making on whether to utilise or discard.

Subnormothermic machine perfusion and controlled oxygenated rewarming

Continuous subnormothermic machine perfusion (SMP) of DCD porcine kidneys has demonstrated improved creatinine clearance and preservation of structural integrity compared to continuous oxygenated HMP and SCS (49). Three hours of controlled oxygenated rewarming (COR) following 18h SCS enhanced creatinine clearance compared to continuous or pre-implantation HMP in a pig reperfusion model (51). Clinical use of SMP or COR in kidney transplantation has not yet been reported.

Liver

Hypothermic machine perfusion

Experimental evidence shows that livers can be preserved by low pressure oxygenated HMP (or hypothermic oxygenated perfusion (HOPE)), using either continuous or pre-implantation perfusion (33). Oxygenated HMP reduces ischaemia-reperfusion injury and protects against biliary injury in preclinical models, however, there is no evidence yet that HMP can extend liver preservation times (29, 67). HMP of discarded human livers confirmed feasibility and safety of the technique (28, 68-70). The Columbia group was the first to report the transplantation of 20 DBD livers preserved by pre-implantation HMP compared to matched SCS-controls (27). Pre-implantation HMP provided safe preservation in this pilot study with low EAD rates (5% vs. 25% of SCS livers). Guarrera *et al.* recently

reported on transplanting “orphan” livers -refused for transplantation by numerous centres- after pre-implantation HMP achieving reduced EAD rates, less biliary complications and shorter hospital stay compared to matched SCS-controls (31).

The initial clinical experience of pre-implantation HMP of eight DCD livers by the Zürich group, showing feasibility of the technique with no evidence of ischaemic cholangiopathy eight months post-transplant despite extended DCD criteria (30) was recently expanded. Dutkowski *et al.* transplanted 25 DCD livers after pre-implantation oxygenated HMP and compared these to a matched cohort of 50 SCS DCD livers where they showed a reduced rate of intra-hepatic cholangiopathy at 1y follow-up and improved 1-year graft survival for pumped vs. SCS livers (32). Further studies comparing pre-implantation HMP with SCS have been announced (Table 2), some using single portal vein perfusion, others targeting dual perfusion. The Columbia system relies on dual flow-controlled perfusion with low pressures and continuous flow over portal vein and hepatic artery, the Zürich team applies pressure-controlled portal vein perfusion with continuous flow. The Zürich group have used both the ECOPS and the Liver Assist device for this purpose (Organ Assist, Groningen, The Netherlands). There are no trials exploring continuous HMP, however, Guarrera *et al.* suggest that prolonged SCS prior to HMP may negatively affect outcomes, therefore they encourage the development of a portable device.

Adequate perfusate oxygenation seems necessary to protect the liver against ischaemia-reperfusion injury (71) although the ideal oxygen tension is unknown. Findings are inconsistent and a balance between beneficial effects of oxygen and production of radical oxygen species is likely to be important (71, 72). There is also debate whether active oxygenation (e.g. by an oxygenator, bubbling oxygen through the perfusate) is needed in the hypothermic setting, as Guarrera *et al.* report perfusate oxygen tensions >120mmHg in an open system without active oxygenation (27).

Viability assessment during HMP is largely unexplored. Bile is not produced during HMP and although perfusate transaminases might correlate with graft injury, data from large clinical trials is needed to determine the value of HMP as a tool to predict outcome (27, 28, 73, 74).

Normothermic machine perfusion

NMP simulates *in vivo* conditions and requires dual perfusion through hepatic artery and portal vein at physiological flows. It is thought to enable organ viability assessment (75, 76), reduce PNF, improve early graft function, and reduce ischaemic cholangiopathy by improved perfusion and preservation of the peri-biliary vascular plexus and peri-biliary glands (37, 41, 42).

After numerous preclinical studies showing benefit of continuous NMP, a phase I study in the UK showed that prolonged continuous NMP with the portable Metra device (OrganOx, Oxford, UK) is feasible and safe (77). Twenty livers, of which 10 had high-risk profiles, were successfully transplanted with 6 month survival similar to that of 40 matched controls. Currently, a large phase III RCT is comparing continuous NMP using the Metra with SCS within COPE (Table 2, Suppl. Appendix 4). The primary outcome is peak AST in the first seven days post-transplant (as a risk factor for graft survival) and the trial will also assess organ discard rates, PNF, EAD, ischaemic cholangiopathy on MRCP at 6 months, and graft and patient survival. Two trials with a different NMP liver device (OCS Liver) developed by TransMedics (Andover, MA, USA) have been started (Table 2), one is a safety study, the other an RCT with EAD as the primary outcome. Another RCT comparing NMP with SCS is running in Cleveland, USA, using a home-made circuit and targeting EAD as primary endpoint (Table 2).

The first case report using pre-implantation NMP of a human liver followed by successful transplantation has recently been published (44). Another case report describes a discarded liver successfully transplanted after assessment by pre-implantation NMP, with the decision to transplant made on the basis of normalisation of lactate (<2mmol/L) and bile production by the graft (78). These two parameters are judged as important markers, although additional research in large trials is needed to confirm this. Animal studies in DCD settings have suggested that continuous NMP is superior to pre-implantation reconditioning with NMP (37), however, if pre-implantation NMP

would prove non-inferior to continuous NMP, perhaps for a certain category of donor livers, this may offer logistical benefits whilst viability-assessment might still be possible (75, 78).

Subnormothermic machine perfusion and controlled oxygenated rewarming

Animal survival, liver function and bile duct preservation has been shown to be better after SMP than SCS in rat and pig models (45, 48, 79-82). Although SMP has not been used clinically, discarded livers can be supported by SMP with adequate flow rates, bile production and various biochemical parameters as potential surrogates for organ viability whilst histological analysis reveals no additional injury due to SMP (46, 47).

Slowly rewarming the liver during COR to 20°C over 3h by pumping hepatic artery and portal vein has been shown to improve tissue energetics and histological appearance in a pig model (50). The first clinical COR-application of 6 high-risk, "orphan" DBD livers showed feasibility of COR with good function at 3 months compared to historical SCS-controls (83).

In situ dynamic preservation or abdominal regional perfusion

Regional perfusion (RP) of abdominal organs in DCD donors applies extracorporeal membrane oxygenation to deliver oxygen after a period of warm ischaemia. Hypothermic RP (HRP) reduces metabolic activity and requirements whereas Normothermic RP (NRP) may support the restoration of cellular processes by constant supply of oxygen and substrates in a near-physiological way (84).

HRP in DCD has shown overall good kidney graft survival (>85%) but PNF could not be avoided and high rates of DGF (up to 75%) have been reported (84). The largest reported series of 320 DCD I+II (failed resuscitation outside or inside the hospital) kidney transplants shows an 87% 1-year graft survival (85). HRP (at 4-10°C) of livers has not been reported. NRP in DCD III has also shown good kidney graft survival with lower DGF rates (between 8% and 42%) (84, 86).

NRP of DCD II+III livers shows a wide range of graft survival rates (43%-91%) but acceptable patient survival (71%-91%) although PNF and ischaemic cholangiopathy incidences are higher than in recipients of DBD livers (84).

Mechanisms of injury and repair during machine perfusion

It is not known how dynamic preservation exerts its beneficial effects but perfusion likely helps to maintain a healthy endothelium, replenish ATP and it might even alter the organ's immunogenicity (87, 88). Increased NO-dependent vasodilation and improved cortical microcirculation at reperfusion regulated through improved eNOS phosphorylation has been demonstrated in HMP-preserved DCD porcine kidneys (89). Moreover, a degree of vascular shear stress, that plays a critical role in normal vascular function, is maintained by the pulsatile flow of HMP, which could have an anti-inflammatory effect through the activation of flow-dependent genes (26, 90).

Oxygenation during HMP has been shown to restore ATP content in kidney (61) and liver (33). In the liver, oxygenated pre-implantation HMP reversibly suppresses mitochondrial oxidative metabolism after cold preservation decreasing the mitochondrial release of reactive oxygen species upon reperfusion with several fold deactivation of numerous intracellular and extracellular pathways, including the host inflammatory response (19, 88, 91). Little is known about the working mechanisms of SMP and NMP besides the attempt to maintain a physiological environment. For blood-based perfusion there is evidence that the absence of leucocytes and platelets limits the inflammatory response and reduces apoptosis (36). A comparison of pre-implantation HMP with pre-implantation NMP of rat DCD livers that were SCS for 4h showed improved survival of both techniques compared to continued SCS after 30 min donor warm ischaemia time. However, when donor warm ischaemia time was 60 min, pre-implantation HMP resulted in improved survival (92).

Multi-platform -omics studies and combination with computational biology will allow the use of an integrated approach to identify new pathways of injury and repair during organ preservation (93).

This will also ease identification of ways to improve dynamic preservation through development of targeted interventions.

How to move forward?

Dynamic preservation has the potential to improve (abdominal) organ preservation. However, there are many questions that remain unanswered today. Dynamic preservation techniques should not only be compared, they should also be evaluated in the light of other optimisation strategies such as e.g. donor hypothermia (94). Furthermore, it has become clear that organs with a different baseline risk will benefit from different preservation methods and graft-tailored conditioning should be the focus of future research. The use of dynamic preservation to resuscitate grafts, not only by restoring oxygen and nutrient flow, but also by actively targeting repair is underexplored as yet. Nevertheless, the addition of specific drugs, gene or cell therapy to an isolated organ and not to a patient is very attractive and has the potential to increase the number of transplantable organs.

Much like organ donor intervention trials (95), organ preservation trials pose many regulatory, legal, ethical, and logistical challenges and those unique to organ preservation trials. At which stage and from whom should consent for research be sought as intended recipients may change following the preservation phase (e.g. due to a positive cross-match or recipient non-transplantability)? How should re-offering of these organs occur when randomisation and treatment of the organ has perhaps already started whilst there remains the inevitable pressure of time? If discarded organs seem to perform well during organ preservation, should they then be re-offered and how should this be done? To facilitate organ preservation research a debate between regulatory authorities and the transplant community is needed. Additionally, financial climate and device costs make it challenging to run investigator driven trials independent from the industry. Nevertheless, the search for optimised graft-tailored preservation and repair is crucial and as important as managing acute rejection was in the early days of transplantation: it deserves to be tackled with high priority and the same urgency.

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Figure Legends

Figure 1: Classical build-up of an *ex vivo* (Panel A) and *in vivo* (Panel B) dynamic preservation circuit. Perfusate is pumped through the organ vasculature by a pump (usually a roller or centrifugal pump). Addition of a heat-exchanger allows to vary the temperature, an oxygenator can be added to the circuit to oxygenate the perfusate. In case of hypothermic dynamic preservation the organ and reservoir are often topically cooled with ice without the need of a heat exchanger. During *ex vivo* machine perfusion (A), the organ sits in an organ chamber that is connected to a reservoir that drains the perfusate. In case of dynamic preservation of the liver, dual perfusion of portal vein and hepatic artery can be established by separately cannulating these vessels. Often a second pump will drive the hepatic artery perfusion (circuit in dotted line) so that different pressure/flow settings can be used. During *in vivo* regional perfusion (B) the pump will drive the perfusate into the donor's arterial circulation, the venous cannulation guarantees return of the perfusate. A heat exchanger and oxygenator can be added to the circuit.

HE, heat exchanger; O2, oxygenator; the arrows denote the direction of flow.

Figure 2: The different dynamic preservation strategies currently entering clinical practice with the different modalities of their use.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1: Non-exhaustive list of planned or on-going clinical trials investigating dynamic preservation of kidney or liver that were not registered in an online clinical trial registry at the time of writing this manuscript.

Supplementary Appendix 1: Search strategy of online clinical trial registries

Supplementary Appendix 2: The trial protocol of the COPE-COMPARE trial comparing continuous oxygenated hypothermic machine perfusion with continuous non-oxygenated machine perfusion in kidneys over 50 years of age donated after circulatory death (Maastricht type III donors).

Supplementary Appendix 3: The trial protocol of the COPE-POMP trial comparing oxygenated pre-implantation hypothermic machine perfusion with static cold storage in kidneys from expanded criteria donors.

Supplementary Appendix 4: The trial protocol of the COPE NMP liver trial comparing continuous normothermic machine perfusion with static cold storage of liver grafts.

Supplementary Appendix 5: Overview of the collection of samples from the clinical trials in COPE.

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Tables

Table 1 Overview of ongoing or planned clinical trials in kidney preservation based on search of online clinical trial registries (see Table S1: Non-exhaustive list of planned or on-going clinical trials investigating dynamic preservation of kidney or liver that were not registered in an online clinical trial registry at the time of writing this manuscript. **Supplementary Appendix 1***).*

Donor type	Preservation	Endpoint	Design	Start	Status	Registration	Acronym	Lead
DBD	piHMP vs. SCS	DGF	RCT	08/2005	Analysing	ISRCTN35082773	HBD Pump	Cambridge, UK – C. Watson
DBD	c/piHMP vs. SCS in normothermic and hypothermic DBD	DGF	RCT	11/2015	Not yet recruiting	NCT02525510	n.a.	San Francisco, USA – D. Malinoski, C. Niemann
DBD ≥50y	HMP	6mo GFR	Observational, case control	06/2016	Recruiting	NCT02055950	PREDICTION	Italy, P. Cravedi
ECD	piHMP	3mo GS	open, non-randomised	10/2011	Recruiting	DRKS00000121	n.a.	Essen, Germany – A. Paul, A. Gallinat
ECD	piHMP+O_2 vs. SCS	1y GS	RCT	05/2014	Recruiting	ISRCTN63852508	COPE-POMP	COPE – A Paul, T. Minor, P. Kocabayoglu, R. Ploeg
ECD	c/piHMP vs. SCS	DGF	RCT	04/2010	Recruiting	NCT01170910	IMPULSION	Lyon, France – L. Badet
DCD III	cHMP vs. SCS	DGF	RCT	04/2011	Recruiting	ISRCTN50082383	CAD-MP	Cambridge, UK – C. Watson, D. Summers
DCD III ≥50y	cHMP+O_2 vs. cHMP	1y GS	RCT	01/2014	Recruiting	ISRCTN32967929	COPE-COMPARE	COPE – J. Pirenne, I. Jochmans, R. Ploeg
Deceased	HMP vs. HMP with eternacept	DGF, 12mo GS	RCT	04/2011	Recruiting	NCT01731457	n.a.	Poland – P. Domagala, A. Kwiatkowski

CAD-MP; cardiac death – machine perfusion; cHMP, continuous hypothermic machine perfusion; COMPARE, cold oxygenated machine perfusion of aged renal grafts; COPE, consortium for organ preservation in Europe; DBD, donation after brain death; DCD, donation after circulatory death; DGF; delayed graft function; ECD, expanded criteria donor; EVNP, *ex vivo* normothermic perfusion; GS, graft survival; HBD, heart beating donor; O_2, oxygen; piHMP, pre-implantation hypothermic machine perfusion; piNMP, pre-implantation normothermic machine perfusion; POMP, pulsatile oxygenated machine perfusion; RCT, randomised controlled trial; SCS, static cold storage

Table 2 Overview of ongoing or planned clinical trials in liver preservation based on search of online clinical trial registries (see Table S1: Non-exhaustive list of planned or on-going clinical trials investigating dynamic preservation of kidney or liver that were not registered in an online clinical trial registry at the time of writing this manuscript.

Supplementary Appendix *1*).

Donor type	Preservation	Endpoint	Design	Start	Status	Registration	Acronym	Lead
DBD	piHMP+O_2 vs. SCS	Postop complications (Clavien-Dindo class III-IV)	RCT	09/2011	Recruiting	NCT01317342	HOPE	Zürich, Switzerland – P. Dutkowski
DCD	piHMP+O_2	6mo GS	Pilot	04/2014	Completed	NTR4493	Dual HOPE	Groningen, The Netherlands – R. Porte
DCD	piHMP+O_2 vs. SCS	IBS on 6mo MRCP	RCT	10/2015	Recruiting	NCT02584283	Dual HOPE	Groningen, The Netherlands – R. Porte
DBD + DCD III	cNMP	30d GS	Historic control	10/2012	Completed	ISRCTN14355416	n.a.	London, UK – N. Heaton
DBD + DCD III	cNMP vs. SCS	Peak AST	RCT	04/2014	Recruiting	ISRCTN39731134	COPE-WP2	COPE, P. Friend, D. Nasralla, R. Ploeg
Deceased	NMP	EAD	Matched controls	07/2015	Recruiting	NCT02515708	n.a.	Cleveland, USA – C. Quintini
Deceased	NMP	Safety	Pilot	06/2015	Recruiting imminent	NCT02449694	REVIVE	Leeds, UK – M. Attia
Deceased	NMP vs. SCS	EAD serious adverse events	RCT	09/2015	Recruiting imminent	NCT02522871	OCS Liver PROTECT Trial	n.a.

cNMP, continuous normothermic machine perfusion; COPE, consortium for organ preservation in Europe; COR, controlled oxygenated rewarming; DBD, donation after brain death; DCD, donation after circulatory death; EAD, early allograft dysfunction; ECD, expanded criteria donor; GS, graft survival; HOPE, hypothermic oxygenated perfusion; ISB, ischaemic-type biliary strictures; NRP, normothermic regional perfusion; MRCP, magnetic resonance cholangio-pancreatography; O_2, oxygen; piHMP, pre-implantation hypothermic machine perfusion; piNMP, pre-implantation normothermic machine perfusion; RCT, randomised controlled trial; SCS, static cold storage

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